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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
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Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/419,817	Applicant(s) HUANG ET AL.	
	Examiner BJ Forman	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *18 October 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-16, drawn to a method to determine a nucleotide, classified in class 435, subclass 6.

II. Claims 17-22, drawn to a pair of primers and a kit containing the primers, classified in class 536, subclass 24.3.

2. The inventions are distinct, each from the other because:

Inventions I and II are related as process of using a product and the product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product i.e. the primers can be used as probes in nucleic acid hybridization assays.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Sarah Kagan on 8 May 2000 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-16. Affirmation of this election must be made by applicant in replying to this Office action. Claims 17-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-16 are indefinite because it is unclear how the last method step of hybridizing relates to the claimed "method to determine a nucleotide at a polymorphic locus". It is suggested that the claims be amended to define the relationship of by inserting a method step for the determination.

b. Claim 10 is indefinite in the recitation "a ratio of nucleotides" because it is unclear what nucleotides are being compared in the ratio. It is suggested that the claim be amended to clarity e.g. "quantities of fluorescent label at known locations on the solid support are compared wherein the known locations represent the presence or absence of an allelic form of a polymorphic locus and from the comparison a ratio of the polymorphic locus in the sample is determined (see specification, page 25, line 30-page 26, line 4).

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 5 & 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986).

Regarding Claim 1, Vary et al. disclose a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample (Column 2, lines 31-38), the method comprising amplifying a region of DNA comprising the polymorphic locus (Example 3, Column 12, lines 19-30 and primers PM and MM), wherein the primer comprises a 3' portion which is complementary to the region of DNA (Column 7, lines 23-26 and Fig. 3A) and a 5' portion which is identical to all or part of a probe on a solid support and not complementary to the region of DNA (Column 7, lines 26-30), labeling the amplified DNA to form labeled amplified DNA products (Column 3, lines 54-60), and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B).

Regarding Claims 5 & 7, Vary et al. teach the method of Claim 1 wherein the nucleotide is radioactively labeled with ^{32}P-dATP (Column 3, lines 54-59) and epitopically labeled wherein the epitope is a halogen-modified nucleotide which is antibody-detected (Column 3, lines 63-65 and Column 4, line 66-Column 5, line2).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 2-4, 6, 8 & 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) as applied to claim 1 above, and further in view of Brown et al. (U.S. Patent No. 5,807,522, filed 7 June 1996), Maniatas et al. (Molecular Cloning: a laboratory manual, 1982, page 148) and Hames et al. (Nucleic Acid Hybridisation: a practical approach, 1988, pages 35, 36 and 42-44).

Regarding Claims 2 & 3, Vary et al. disclose the method of Claim 1 but they do not teach the labeling couples a labeled nucleotide to the 3' end. Brown et al teach a method to determine a polymorphism in a sample the method comprising, amplifying a DNA region comprising a polymorphic loci, labeling and hybridizing the amplified product to probes on a solid support (Column 15, lines 27-47) wherein the labeling attaches a labeled nucleotide to the 3' end (Column 15, lines 35-48 and Column 16, lines 47-54). Brown et al. teach labeling using standard means as taught by Maniatas et a. who teach labeling 3' ends of nucleotides using terminal transferase (page 148). Additionally, it was known in the art that terminal transferase specifically labels 3' end (see Hames et al. page 35-36). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teachings of Brown et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the incorporated labels of Vary et al. with the 3'end labeling of Brown et al. for the known benefit of terminal transferase specificity and for the obvious benefit of reducing the amount of labeled nucleotides required.

Regarding Claims 4 & 6, Vary et al. do not teach the nucleotide is labeled with fluorescence. However, Brown et al. teach the nucleotide is labeled with fluorescence (Column 15, lines 35-38) and they teach the fluorescent label is detected optically on the solid support

(Column 15, lines 35-38 and Column 14, lines 11-18). Vary et al. and Brown et al. do not teach the nucleotide is labeled with an enzyme. However, enzymatically labeled nucleotides were known and routinely used in the art as taught by Hames et al. who teach the attachment of enzyme labels to nucleotides wherein the enzyme labeled nucleotides are safe, highly sensitive, inexpensive and allow rapid detection (pages 42-44). Therefore, It would have been *prima facie* obvious to one of skill in the art to modify the method of Vary et al. with the teaching of Brown et al. and Hames et al. to obtain the claimed invention because one of skill in the art would have been motivated with a reasonable expectation of success to apply the labels and detection of Brown et al. and Hames et al. for the obvious benefit of efficient, convenient and economic labeling.

Regarding Claims 10-13, Brown et al. teach the detection of Claim 8 above wherein the fluorescently labeled nucleotides at known locations on the solid support are compared and the ratio of the compared nucleotides determines the presence or absence of a mutation e.g. polymorphism (Column 15, lines 8-22) and they teach the ratio of nucleotides at two or more polymorphic loci or two or more DNA regions are determined simultaneously for two or more individuals i.e. "many patients against all known mutations in a disease gene" (Column 15, lines 19-22). It would have been ***prima facie*** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teachings of Brown et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to modify the method of Vary et al. wherein a region of DNA is analyzed by the Brown et al. method wherein multiple loci, and multiple individuals are analyzed simultaneously for comparison and wherein a ratio is derived from the comparison and used to determine the presence of a polymorphic locus for the obvious benefits of eliminating the additional steps of quantitative analysis and for the

expected benefit of multiple screening i.e. reduced time labor and expense as taught by Brown et al (Column 15, lines 41-43).

Regarding Claim 16, Vary et al. do not teach the method of Claim 1 wherein the solid support is a high density array. However, Brown et al. teach the solid support is a high density array i.e. microarray (Column 6, lines 32-37). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Vary et al. with the teachings of Brown et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to apply the high density array teaching of Brown et al to the method for of Vary et al. for the obvious benefit of analyzing a plurality of DNA regions simultaneously as taught by Brown et al. (Column 15, lines 19-22)

12. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) as applied to claim 1 above, and further in view of Brown et al. (U.S. Patent No. 5,807,522, filed 7 June 1996) as applied to claim 1, 4, & 8 above, and further in view of Okayama et al. (J Lab. Clinical Medicine, 1989, 114(2): 105-113). Vary et al. teach the method of Claim 1 wherein multiple primers are used i.e. MM and PM (Column 12, Example 3) and they teach each primer terminates at a distinct 3' nucleotide (Column 10, Table A, see MM-23 and PM-23)and each 5' portion is identical to all or part of a distinct probe on a solid support (Column 71, lines 26-30 and Fig. 3). Vary et al. do not teach the method comprising two primer pairs. However, Okayama et al. teach a similar method to determine a nucleotide at a polymorphic locus wherein two primer pairs are used. Specifically, Okayama et la. teach amplification of a region of DNA using two primer pairs i.e. the first pair is the Z allele primer plus the distal extension primer and the second pair is the M allele primer plus the distal extension primer (page 108, Fig. 1) wherein the first primer of each pair terminates at a

distinct 3' nucleotide i.e. codon for amino acid position 342 (pages 106-108 and Fig. 1). It would have been *prima facie* obvious to one of ordinary skill in the are at the time the claimed invention was made to modify the method of Vary et al. with the teaching of Okayama et al. to obtain the claimed invention because one of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the primer pairs of Okayama et al. wherein the polymorphic region of DNA is exponentially amplified to the method of Vary et al for the obvious benefit of rapidly and specifically detecting a polymorphism from a crude sample as taught by Okayama et al. (page 112, last paragraph).

13. Claims 14 & 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) as applied to claim 1 above, and further in view of Lockhart et al (U.S. Patent No. 5,556,752). Vary et al. teach the method of Claim 1 wherein the probe is on a solid support (Column 4, lines 44-52) but they do not teach the solid support is a microtiter dish or beads. However, probes immobilized on microtiter dishes and beads were known and routinely used in the art at the time the claimed invention was made as taught by Lockhart et al. who teach a nucleotide detection method wherein probes are immobilized on a solid support wherein the support is beads (Column 7, lines 27-33) and microtiter dishes i.e. a polystyrene support having depressed regions (Column 8, lines 41-44 and 50). It would have It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the solid support of Vary et al. with the teachings of Lockhart et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to apply the solid support teaching of Lockhart et al. wherein probes are immobilized on microtiter dishes and beads for the obvious benefit of immobilizing probes in regionally defined and separate areas and thereby identification of hybridized nucleotides based on the region of hybridization.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
May 15, 2000

S. Stamer

PRIMARY EXAMINER